Journal of Surgical Oncology 1999;71:198–205

REVIEW ARTICLE

Biological Considerations With Pelvic Neoplasms

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The strategy of therapy for any neoplasm is determined to a significant degree by the biological characteristics of the neoplasm. The ones benefited most by surgical ablation are the cancers that grow locally but never metastasize. The second group is composed of neoplasms with exceedingly slow growth rates permitting long periods of symptom-free survival before recidivation. Many such cancers occur in pelvic structures requiring understanding of the nature of the cancers and then techniques necessary for their resection. The review provides an introduction to some of the relevant biological considerations.

J. Surg. Oncol. 1999:71:198–205.

KEY WORDS: **metastasizing, nonmetastasizing tumors; medullary cancer; recurrent cancer; peritoneal metastases; pseudomyxoma peritonei; urinary bladder; cervix uteri; endometrium; chondrosarcomas; sacrococcygeal chordomas; radiobiological changes; pelvic surgery**

INTRODUCTION

This review will consider the biological properties of neoplasms of the pelvis associated with sustained local growth, but no metastases or limited intrapelvic metastases. Many of the neoplasms under consideration evolve slowly [1,2]. Despite the advanced state they can attain, there is still the opportunity for surgical control or significant palliation. When a neoplasm is encountered that has attained extensive local size, but has not metastasized to an extrapelvic site, one may assume, on clinical grounds alone, that a chronic, local nonmetastasizing neoplasm is present that may be amenable to control by surgical resection. Successful surgical ablation of these neoplasms requires careful preoperative evaluation and planning to ensure that a definitive operation can be done that will encompass the neoplasm and all contiguously involved structures, with a margin of normal tissue. Preoperative imaging studies will help delineate the extent of the neoplasm.

ADENOCARCINOMAS OF THE RECTUM AND COLON

Adenocarcinomas of the rectum and colon are characterized by a spectrum of biological behavior [3]. Their rate of growth is generally slow and many are present for years before they produce symptoms. In fact, symptoms and earliness are mutually exclusive terms. Though delay in diagnosis after the onset of symptoms is not espoused, if survivorship is measured from the onset of symptoms to correct for lead time, neither patient delay nor physician delay alters the prognosis. This fact has been confirmed in several clinical series and reviews [4–7].

The observation that the probability of metastases from colon cancers to lymph nodes is independent of the size of the cancers is relevant in this phenomenon [8]

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Accepted 6 April 1999

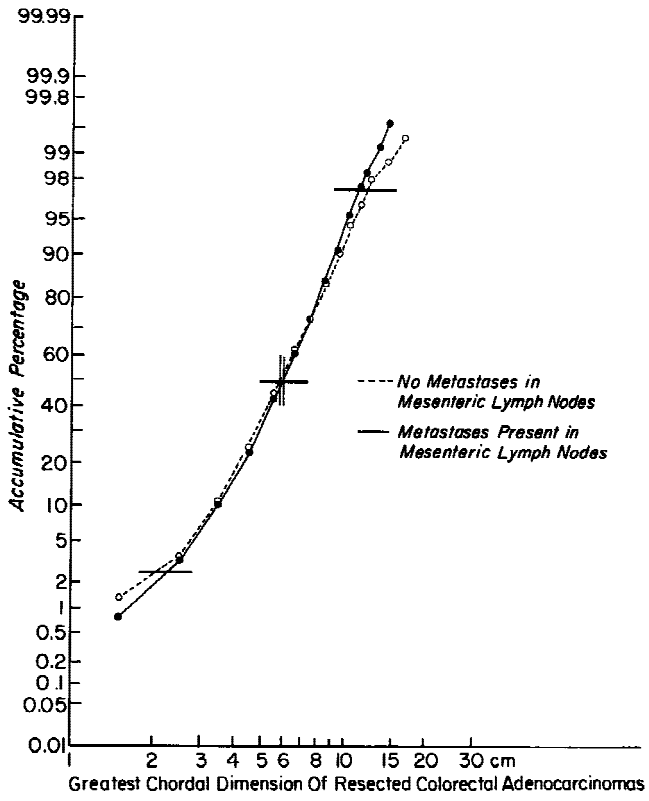

Fig. 1. The greatest chordal dimension of colorectal adenocarcinomas, with and without metastases in the mesenteric lymph nodes is plotted against the accumulative frequency. The median chordal dimensions for the two distributions are 6.1 and 6.2 cm. The 99% confidence range for the size of cancers with metastases was 19.4–0.9 cm, and without metastases, 20.3–0.9 cm. There was no significant difference between the two means ($P > 0.9$) or between the variances ($P > 0.99$). Reprinted with permission from Spratt JS Jr: The longnormal frequency distributions and human cancer. J Surg Res 1969;9:151–157.

(Fig. 1). This observation has been confirmed in several series [3,9]. One of the first controlled clinical trials completed by the National Surgical Breast and Bowel Project corroborated this observation [9].

After numerous studies of the relationship between cytological features and prognosis of colorectal cancers, the ability to stratify these cancers further is still limited. Deoxyribonucleic acid (DNA) ploidy has been associated with relatively poor prognosis in some studies, but not in others [10,11]. Disagreement on prognostic efficacy may be attributed, at least in part, to heterogeneity of DNA-content stemlines in colorectal carcinoma, which makes results sensitive to sampling techniques [12].

Lanza et al. [13] have shown prospectively that DNA ploidy status is a significant and independent prognostic factor with colonic cancers. Diploid cancers showed significantly better disease-free and overall survival rates for both stage II and stage III cancers. In fact, the stage II diploid cancers had an overall 5-year survival rate of 97%. For cancers of the proximal colon, the ploidy status was the most significant prognostic variable [14]. Kato et al. [15] have recently reported assessment of silver-staining nuclear organizing region (AgNOR) counts, showing poor outcome with a combination of DNA-aneuploidy and high AgNOR score. The prognostic utility of DNA ploidy may depend on technique. From time to time, papers appear which deny the prognostic importance of DNA ploidy against a consensus that ploidy is prognostic [16]. Tumors of the right side are more often DNA diploid and are associated with DNA repair errors and relatively good prognosis [17]. Growing insight into cytological properties should correlate with observations from retrospective surgical series of very favorable outcomes with resected large colorectal cancers. Most cancers have developed their heterogenous nature, which will determine their behavior before they become detectable.

Rates of neoplastic cell proliferation measured by different techniques have or have not correlated with outcome [16]. Meyer and Prioleau [17] determined the S-phase fraction (SPFs) of 100 resected colorectal neoplasms by in vitro exposure to tritiated thymidine with autoradiography. The frequency distribution of the SPFs was Gaussian with a median of 17.8 per 100 in 90 unirradiated carcinomas and 6.9 for 10 carcinomas that had been irradiated before resection. For the unirradiated cancers, they were unable to show a relationship between the SPF sex, site, size, Dukes stage, number of mesenteric lymph nodes containing metastases, presence of adenomas, overall and relapse-free survival, nor SPF values for adjacent normal colorectal crypts. The spatial evaluation showed many nonproliferative cells. The authors suggested that this might affect the response to radiotherapy [17]. These SPF values would equate to very short potential doubling times. However, surface desquamation alone would greatly lengthen the actual doubling time.

Phenotypic markers for aggressiveness may from time to time be discovered. The carbohydrate antigen CA 19-9, which binds to endothelial cell surface receptors, may be useful. Nakayama et al. [18] found that expression of this antigen in tumor tissue or serum was an indicator of mortality after resection of colorectal carcinoma.

Correlation of genetic, as well as cytometric, analysis with prognosis is an evolving field of potentially great value. As an example, Jen et al. [19] have noted that patients with stage II colorectal cancers and chromosome 18q allelic loss have survival rates similar to that of patients with stage III cancers. The latter are reported to benefit from adjuvant chemotherapy. Patients with stage II disease not associated with chromosome 18q allelic loss had excellent survival rates and probably may not need adjuvant therapy. Progress has been rapid in defining genetic abnormalities of colorectal carcinoma and cells can follow a number of different pathways to cancers with different biological behavior.

Costa et al. [20] have reported studies on the association of cell proliferation-related markers and prognosis with hepatic metastases from colorectal neoplasms. The thymidine labeling index (TLI), DNA ploidy, and the expression of p53 and bel-2 measured by immunohistochemistry, were measured. Only TLI was a significant indicator of relapse-free survival at 4 years after surgical resection of metastases. Cancers with high TLI had a 100% recurrence rate within 4 years.

The contributions of chemotherapy or radiotherapy to cancers with an inherently low proliferation index and a longer symptom-free survival time have yet to be confirmed. The surgical ablation of these cancers and their metastases, with an adequate surgical margin, when possible, remains essential—either for control or for protracted periods of symptom-free survival.

The early evolution of the cytological composition of a cancer gives insight into observations that the probability of metastasis is independent of the size of resected cancers, and prognosis also is independent of the size of resected cancers. A colorectal adenocarcinoma that produces symptoms typically is a comparatively large cancer with well-established cytological properties. The ability to predict prognosis based on the cytological properties of cancers and their metastases may, in time, enhance the accuracy of identifying patients who do and do not need adjuvant therapy and who offer the best chance for curative surgical ablation.

The colon is exposed on a lifelong basis to genomic damage of its mucosa. In 1965, Spjut and Spratt [21] demonstrated similarity in the distribution and type of neoplasms induced in the colon of rats exposed to a carcinogenic aromatic amine to the observed distribution and type of neoplasms occurring in man. The ability to quantify the extent of genomic damage produced in the cells of colonic neoplasms has now advanced to the point that these measurements may be useful in predicting the prognosis with colonic neoplasms [22].

The potential for separating those cancers controllable by surgery alone from those that might also benefit from adjuvant therapy, may be attainable by quantifying the extent of genomic damage. This is a real possibility for the future and would be of great economic and clinical value. Correlation of the variance in molecular and genetic markers with prognosis was identified as an important area of research in future clinical trails by Vaughn and Haller [23].

Presently, only those tumors anatomically favorable to complete surgical ablation may be considered curable. Radiotherapy delays local recurrence and research is ongoing with respect to the most effective combination of chemotherapy agents for delaying recurrence and enhancing survival. Parallel analysis of pharmaco-economics and quality of life are also in progress. Since this is an area of research in progress and many studies have not reached a level of statistical significance, the pelvic surgeon's role remains one of ensuring complete surgical ablation, and insistence on accurate pathological assessment of margins of resection and nodal status. Studies of potentially prognostic attributes which may include tumor ploidy, S-phase and growth fraction, and newer molecular markers of prognostic significance should be pursued as they become available. The contribution of adjuvant therapies to outcome will increasingly be quantifiable with respect to specific subsets of colonic neoplasms along with considerations of cost with respect to benefit.

The extent of actual resection is determined by the extent of the neoplasm, and requires technical knowledge of a variety of operations that often can be divided into subroutines combined and sequenced in ways determined by the extent of the cancer and the postablative reconstruction. Selection of the appropriate operation also requires sound knowledge of pelvic anatomy [24].

Examples of operations include anterior, posterior, and total pelvic exenterations sometimes contiguous with the musculoskeletal pelvis, which must be removed en bloc by partial or total resection, reconstruction of the urinary tract and colon with appropriate drainage and rehabilitation, and, rarely, hemicorporectomy.

Not only is the survivorship of patients with colon cancers that are resected not favorably influenced by the small size of the primary cancer, but survivorship is better with very large cancers that are resectable [3]. This seeming paradox is probably explainable by a selection bias. As the cancers grow, those destined to metastasize will have manifested this potential by the time cancers attain the larger size and are deemed either inoperable or unresectable.

To help identify cancers that fall into the metastasizing and nonmetastasizing subsets, the characteristics of the two subsets were compared, and the results are shown in Table I [25]. Nonmetastasizing cancers may invade contiguous viscera. The effective resection of these advanced local cancers requires en bloc exenterative procedures for all involved organs. Exposed cancer may implant and incompletely excised ones will recur locally. Control of locally recurrent cancers may require even more extensive resection.

Before a second resection for recurrent colorectal cancers is undertaken, the pathological characteristics identified in the primary cancer removed at the first resection must be reviewed. There are certain characteristics that are associated with an incurable cancer, and the second effort will also fail with these variants. The ineffective second attempt simply may compound the patient's terminal morbidity. The adverse characteristics identified are "signet ring" cancers, metastases in more than six mesenteric lymph nodes, undifferentiated (grade III) cancers other than medullary, and cancers with extensive

TABLE I. Characteristics of Resected Colorectal Cancers With Significant Presence or Absence of Lymph Node Metastases*

Associated with lymph node metastases	Associated with no lymph node metastases
Past or present associated cancer of the skin	Absence of proven or suspected metastases outside field of resection
Resected with proven or suspected distant metastases	Microscopic margin "pushing" (well circumscribed or mixed)
Incomplete local resection	Deep margin of cancer through inner muscle
Microscopic margin infiltrating	
Deep margin into muscle	Deep margin of cancer into mesenteric fat
Less inflammatory reaction	Direct extension into adjacent organs
Cancer in blood vessels or lymphatics near primary	

*Adapted with permission from Spratt JS, Watson FR, Pratt JL: Characteristics of variants of colorectal carcinoma that do not metastasize to lymph nodes. Dis Col Rect 1970;13:243–246.

lymphatic and perineural invasion. In the stomach, medullary cancer has been a term applied to tumors considered to be a solid variant of intestinal form of adenocarcinoma. Colorectal cancers of the medullary type of poorly differentiated adenocarcinoma proved to have a better prognosis than the more pleomorphic type of poorly differentiated cancer. Of 13 medullary carcinomas, only 1 was DNA-aneuploid compared to 5 of 7 of the pleomorphic type. Medullary carcinomas are composed of uniform cells, small-to-medium nuclei, prominent nucleoli, circumscribed borders in most, and Crohn-like inflammatory infiltrate at the borders. The pleomorphic variant is infiltrative, has coarse chromatin, and atypical mitoses (26).

Kim et al. [27] found medullary cancer expressed replication error phenotype (microsatellite DNA sequence length variations). It is estimated that approximately 5–10% of colorectal cancers in hereditary nonpolyposis colon carcinomas (HNPCC) are poorly differentiated medullary type. The majority of both types of undifferentiated cancers in this series were proximal to the splenic flexure. Only one patient with uniform medullary cell type died of metastatic disease during a median 31-month follow-up, but five of seven patients with pleomorphic type died. Microsatellite instability was almost totally restricted to the medullary type (100% vs. 14.3%, $P < 0.001$). None of the medullary type showed stabilization of p53 protein (0/13), whereas 43% of the pleomorphic group showed stainable p53.

Unless there exists an adjuvant therapy protocol with promise, the outlook for patients having recurrent cancers is dismal, and only palliation of symptoms can be offered. The worst possible end stage occurs when a patient develops a perineal fistula, which is best managed, when possible, by isolation of the fistulous intestine with a bypass procedure that leaves the fistulous intestine undisturbed in the pelvis. The afferent and efferent ends of the intestines continuous with the fistula are brought to the surface with drainage stomas and intestinal continuity is restored, bypassing the fistula. Dissection of the fistulous intestine from the deep pelvis in the presence of either recurrent cancer or extensive pelvic irradiation is exceedingly difficult and of no or only transient benefit to the patient. The intestine falls back into the pelvis and the fistula often recurs or intestinal obstruction develops. One technique that may deter the latter development in some is the rotation of a muscular pedicle to fill the dead space and buffer the intestines from a recurrence of deep pelvic attachment and recurrent fistula formation.

When a primary colorectal adenocarcinoma has been resected and the resection has removed all gross disease offering the possibility of cure, some cancers will still recur locally and develop distant metastases. When the colorectal carcinomas are resected with the intent for cure, the log mean time to the diagnosis of recurrence among those that do recur is 17 months with a range from 8 to 36 months with two standard deviations in a log normal frequency distribution of recidivism [28]. These data are derived from series of patients treated by surgery alone with no adjuvant therapy. The pathological determinants of primary cancers likely to be associated with local recurrences without distant metastasis were a mixed pushing and infiltrating margin, and less than six positive lymph nodes in resected mesentery, with no inflammatory response. If the cancers produce carcinoembryonic antigens (CEA) and the CEA rises slowly postoperatively, a resectable recurrence may be present. CEA has not generally proven cost-effective and a rising CEA generally gives about 5 months of lead time before symptoms develop. A rise of more than 50% in brief follow-up periods is usually associated with extensive cancer. Non-CEA-producing cancers may progress with no rise. The earliest symptoms of recurrence are a dull aching discomfort or pain and weight loss. Careful physical examination for palpable masses, chest X-rays, and computed tomography (CT) scans may demonstrate local, thoracic, and hepatic metastases. Occasional pulmonary or hepatic metastases may be resectable [27].

The primary management of perforated and obstructing cancers mandates resection when possible with a delayed anastomosis [29,30]. Cancers that obstruct have usually penetrated the outer longitudinal muscle layer, interrupting longitudinal peristalsis. If perforated cancers are not resected, they seed metastases on the peritoneum as associated infection is controlled.

When colon cancer produces a metastasis in the abdominal wall and no other metastases are known to exist,

the abdominal wall implant may be resected. The incision for resection must be through the abdominal wall away from the metastasis so the surgeon's hand can be inserted and the abdominal cavity and deep surface of the implantation can be palpated. The discovery of multiple peritoneal metastases would generally negate further resection. If the abdominal wall recurrence seems localized, then removal of the full thickness of the abdominal wall with a margin of normal tissue around the metastasis is indicated.

PERITONEAL METASTASES AND PSEUDOMYXOMA PERITONEI

A variety of neoplasms of the abdomen and pelvis have a predilection to produce metastatic seeding of the peritoneum. A variant of this problem produces pseudomyxoma peritonei [31–35]. This syndrome has been the subject of a number of detailed studies paralleled by a more general consideration of the role of intraperitoneal chemotherapy, with or without concurrent hyperthermia. There are no controlled clinical trials confirming survival benefit, but there are generalizations evolving that permit understanding and palliation. Cancer growth on the peritoneal surface tends to fall into two subsets. Categorization requires peritoneal biopsy. In one case, the cancer cells grow on the peritoneal surface as a single layer of cuboidal cells. In the second instance, the cancer on the peritoneum exhibits subserosal invasion with mucous lakes. In both subsets, mitoses are infrequent and the establishment of a cell culture requires a large inoculum and a prolonged period of incubation. None of the tumors we were able to culture exhibited in vitro sensitivity to any chemotherapeutic agent. This low level of chemosensitivity, as well as resistance to radiation therapy, has been observed clinically. However, protracted periods of palliation can be obtained at laparotomy by evacuating all mucinous ascites, resecting the omentum that frequently is studded with neoplasm, stripping out involved strips of peritoneum, and copiously irrigating the peritoneal cavity. Because of the theoretical possibility that some tumor cells may be lysed by heat, we irrigate with 5% dextrose in water (D5W) heated to 55°C for 3 to 5 min only. The D5W is used because of the theoretical possibility that more cells would die with osmolysis than would using normal saline. Although we have used a perfusion system [34], the highest temperature solution for only 3 min is equivalent to lower temperatures for longer periods of time. The same irrigation can be used after any abdominopelvic cancer operation where peritoneal metastases may have occurred. Markham [36] has reviewed the current evolving status of intraperitoneal therapy for gastrointestinal cancer.

The viscous nature of the ascitic fluid associated with pseudomyxoma peritonei precludes adequate evacuation by paracentesis. Thus, periodic laparotomies may be required to evacuate the ascites and again irrigate the peritoneal cavity to remove all of it as completely as possible.

URINARY BLADDER

Cancers of the urinary bladder often reach advanced states either before diagnosis or by intravesical recurrence. Several considerations influence the extent of a definitive surgical procedure. First, the urothelium of the bladder and urethra may exhibit the field effect in the urothelium associated with multicentric cancers. Second, the bladder is a thin-walled viscus and cancers may extend through the wall. Except for cancers on the dome of the bladder, the cancers first penetrate into the perivesicle fat. Anatomically, this fat lies between the visceral fascia on the bladder and the endopelvic fascia on the pelvic parietes. This fat pad must be resected en bloc with the bladder by an anterior pelvic exenteration. The lymph nodes are removed incidentally in the fat pad so dissected. To avoid urethral recurrence, abdominoperineal resection of the urethra en bloc with the prostate (in men) and anterior vaginal wall in women may be required [37].

Supralevator cystectomies leave the urethral epithelium intact, as a focus of additional neoplasms. Both the female and male urethra can be resected en bloc with the bladder by the combined abdominoperineal approach. Implantation metastases can occur if the bladder is accidentally opened or a supralevator transection is done. As a precaution against spillage and implantation, intravesical formalin was previously instilled into the bladder, when operability was confirmed. Povidone iodine has now been substituted for the formalin because it has adequate cytocidal effects and does not have the side effects of formalin. With the use of either, operability must have been confirmed and both ureters ligated to prevent reflux.

CERVIX UTERI AND ENDOMETRIUM

The dominant indications for exenterative surgery for carcinomas of the cervix uteri and endometrium are central pelvic recurrences or primary cancers too advanced to be resected by a lesser operation or controlled by radiotherapy. Seen less frequently today than in the past is central pelvic radiation necrosis, often with fistula formation. Recurrence after radiotherapy is a risk for a protracted period of time after completion of treatment. The survival data on the effectiveness of pelvic exenteration for these cancers clearly documents the value of surgical therapy [24].

CHONDROSARCOMAS

The very slow, but sustained, growth that pelvic or upper femoral chondrosarcomas can attain is shown in Figures 2–5 [38]. The young woman pictured first refused surgery for religious reasons, but the chondrosarcoma continued to grow with a tumor volume doubling

Fig. 2. Gross appearance at time of biopsy of a chondrosarcoma of the femur in a 19-year-old girl (diameter, 15 cm). Reprinted with permission from Spratt JS: The rates of growth of skeletal sarcomas. Cancer 1965;18:14–24, p 21, figure 10.

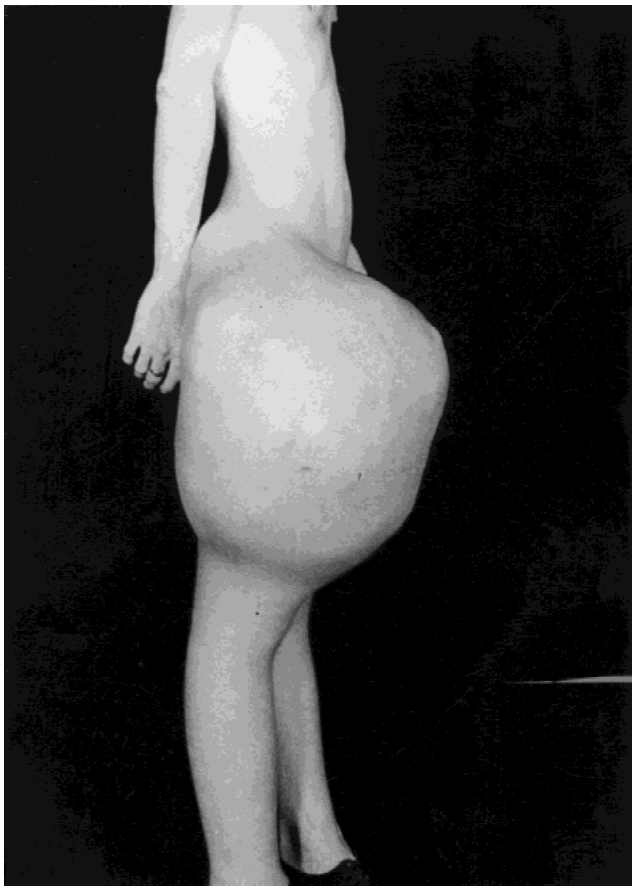

Fig. 3. Gross appearance of chondrosarcoma shown in Figure 1 after 1,200 more days of growth (20 cm diameter). Reprinted with permission from Spratt JS: The rates of growth of skeletal sarcomas. Cancer 1965;18:14–24, p 21, figure 10.

time of 366 days. By the time she consented to an operation, a hemipelvectomy was required which resulted in controlling the neoplasm and long-term survivorship with no metastases or local recurrence. The most important predictors for outcome are adequacy of surgical margins and tumor grade. Sheth et al. [39] made similar observations with respect to chondrosarcomas. Again, inadequate surgical margins were the major factor for local recurrence. High-grade neoplasms often recurred or metastasized in spite of adequate surgical margins. Thus, adjuvant systemic therapy should be considered for high-grade lesions. Sheth et al. [40] have defined the prognostic difference attributable to differentiation for osteosarcomas. Hypervascularity shown on an angiogram defines the high-grade component of these sarcomas. A selective needle biopsy of the hypervascular portion may confirm that a high-grade cancer is present. Preoperative chemotherapy should be considered for the high-grade neoplasms. For low-grade neoplasms, surgical resection with adequate margins gave the optimum patient outcome.

SACROCOCCYGEAL CHORDOMAS

Sacrococcygeal chordomas constitute an infrequent but challenging problem for the pelvic surgeon, and no single surgeon, except on tertiary referral, will see more than several in a lifetime of practice. Chordomas are of low grade histologically, but have a great propensity to metastasize and recur locally; and in our experience, their response to either chemotherapy or radiotherapy is transient [41].

A review of 12 patients suggests the importance of resecting chordomas with a clear margin and no spillage. Current imaging technology should lead to a precise delineation of the extent of chordomas preoperatively. With careful dissection, adequate margins, and no spillage, the prognosis may be improved. Ozaki et al. [42] filled the surgical cavity from which chordomas had been resected with gentamicin beads, then covered it with a gluteal muscle flap. The beads were removed 3 months postoperatively. The contribution of the beads in controlling cancer is unclear.

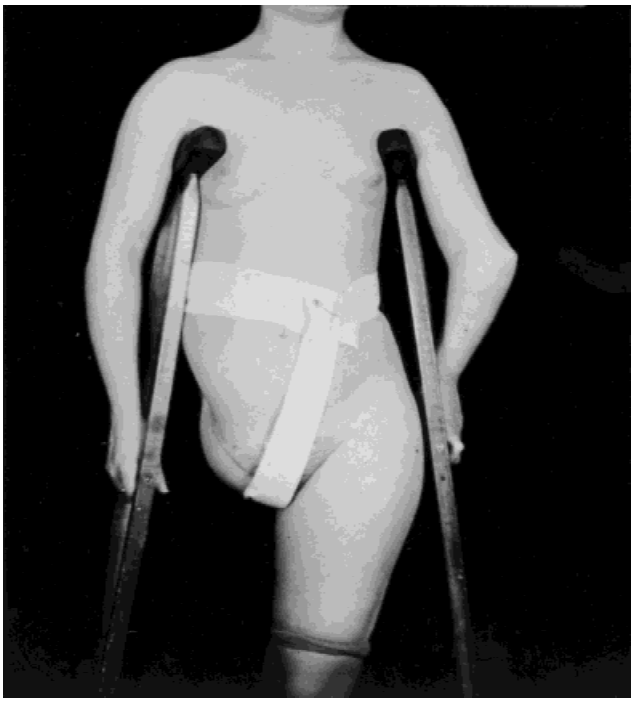

Fig. 4. Gross appearance after 1,470 days of growth from first observation (23 cm diameter). Reprinted with permission from Spratt JS: The rates of growth of skeletal sarcomas. Cancer 1965;18:14–24, p 21, figure 10.

Fig. 5. Gross appearance of chondrosarcoma after hemipelvectomy with skin removed for exposure. Reprinted with permission from Spratt JS: The rates of growth of skeletal sarcomas. Cancer 1965;18: 14–24, p 21, figure 10.

RADIOBIOLOGICAL CHANGES AND SURGERY IN THE PELVIS

Numerous neoplasms of the pelvis are treated primarily, adjunctively, or palliatively by radiation therapy. This treatment produces permanent biological changes in pelvic tissues that must be understood by surgeons who perform major pelvic surgery. Since these changes are dependent on source, time-dose, and field, the surgeon must obtain accurate information from the radiotherapist as to the exact location of the fields of treatment and the type of radiotherapy and the time-dose factors. Location of entry and exit fields must be taken into consideration in planning the incisions, the construction flaps, and the location of anastomoses and stomas. If radiotherapy is to be given postoperatively, the same considerations exist. The surgeon needs to know the planned location of fields so that stomas are not placed in the future site of radiotherapy. Incisions are never angulated in the field sites, and the base of pedicles for reconstruction must not be in the fields. Incisions in irradiated tissue may heal, but healing is much slower.

The reasons for these precautions are well-documented. The endothelium of the microvasculature is very radiosensitive and sclerosis and occlusion occurs, coupled with a reduced capacity for the vascular budding essential for granulation tissue formation and anastomotic revascularization of the tissues. Host sensitivity to radiotherapy also is variable and, therefore, never totally predictable. Thus, the same precautions must be taken in all surgical operations in tissues that have been or will be irradiated.

The present availability of simulators and supervoltage delivery systems producing less lateral scatter is avoiding many catastrophes of the past attributable to overlapping fields, inaccurate dosage calculations, and the "hot spots" that often produced necrosis and intense scarring.

The sclerosis of the microvasculature is subject to progressive occlusion of vessels over time, making irradiated tissues even more ischemic. With trauma, as from an ill-placed biopsy or infection, the process of occlusion may accelerate to the point that major tissue necrosis becomes a serious problem. If the field of necrosis is wide enough, or over a bony surface, contracture—a major component of wound healing—cannot occur. When this occurs over major vessels or other vital structures, catastrophic morbidity can result. Often the only effective surgical approach requires the rotation of a well-vascularized pedicle that has the capacity for vascular budding and fibroblast penetration into the area of radioischemic tissue and areas of radionecrosis. The potential for this source of morbidity requires careful planning of surgical intervention to minimize the risk [43,44].

SUMMARY

An exhaustive review of advanced neoplasms of the pelvis that may require exenterative surgical procedures for control is not necessary, because survival statistics previously reported confirm the efficacy. When a large or advanced neoplasm is encountered with no extrapelvic metastases, it may still be controlled by appropriate surgical operations.

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